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Intranasal Dexmedetomidine increases the successful sedation of children with autism for out-patient auditory brainstem response hearing tests

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ABSTRACT

Introduction: The auditory brainstem response (ABR) hearing test can be challenging in children with autism spectrum disorder (ASD) due to the inherent behavioral challenges associated with this condition. To attempt to increase our success in sedating ASD patients, we added the use of intranasal Dexmedetomidine (Dexmed) to be used alone or with oral Chloral Hydrate (CH) in an ambulatory care setting, with monitoring by a specialist nurse.

Objectives: To determine the success and safety of a protocol for ABR testing performed under sedation with intranasal Dexmed and oral chloral hydrate in ASD patients. To compare the success rate, the occurrence of adverse events and time needed to initiate ABR between Dexmed-CH protocol and previous CH-alone protocol in ASD patients.

Methods: Retrospective review. ASD patients in Dexmed-CH sedation protocol were age- and sex-matched to ASD patients who underwent CH-alone sedation protocol, for comparison.

Results: 74 ABR records in ASD children were included, 37 patients using Dex-CH protocol and 37 patients using CH-alone protocol. In the Dexmed-CH protocol group, Dexmed was used in 2 different ways: alone as a first choice in patients who refused to swallow CH (9/37), or combined with CH as a rescue (28/37). Under this sedation protocol, 89% of the attempted ABRs were completed successfully with no major adverse effects. In comparison, in ASD patients sedated using the protocol of CH-alone, the success rate significantly lower (69% vs. 89%). The time needed to initiate the test was not significantly different.

Conclusion: The use of intranasal Dexmed by itself or in combination with CH was a safe and reliable method of performing sedated ABR in ASD patients. Modifying our previous oral CH protocol to include intranasal Dexmed, substantially improved our success rate of sedation in ASD patients in an ambulatory setting. This study may be of significant value to centers worldwide exploring alternatives to general anesthesia for ABR testing in ASD patients.

1. Introduction

The relationship between autism spectrum disorder (ASD) and hearing loss has been difficult to determine. In a systematic review, Beers at al [1] could not find consensus on whether or not a true relationship exists between peripheral hearing loss and ASD. However, it has been demonstrated that when ASD and hearing impairment coexist, and the diagnosis of one condition often leads to a delay in diagnosing the other [2]. Therefore, a complete audiological assessment is highly recommended in all cases where ASD is suspected. Audiological behavioral assessment in children with ASD can be very challenging due to the nature of the illness. Furthermore, audiologists must often use adapted procedures and may need to rely on less specific measures such as speech audiometry alone or behavioral audiometry [3]. Therefore, the reliability of behavioral hearing assessment results in children with ASD is questionable [4], and more objective tests must be performed to verify these test results.

Tone-burst Auditory Brainstem Response (ABR) is the best tool available in cases where it is not possible to obtain reliable behavioral assessment data [5]. In order for the ABR to yield reliable results, the

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child must be completely still or asleep. For ASD children, this typically requires formal sedation. Since 2004, ABRs have been routinely conducted at our center in the ambulatory care setting using oral chloral hydrate (CH), under the supervision of a trained sedation nurse. However, sedation using CH in ASD patients is challenging for many different reasons. Among these, it requires at least partial cooperation from the patient to swallow the drug. Also, ASD patients are typically older and may be hyperactive, consequently making sufficient sedation using CH difficult to achieve. For these reasons, we have had several cases of sedation failure in ASD children at our center, requiring subsequent general anesthetic in the operating room (OR) in order to complete ABR testing. These experiences have led us to amend our protocol to include Dexmedetomidine (Dexmed), which we use either alone or in combination with CH (Dexmed-CH) when sedation is challenging.

Dexmedetomidine is a potent and highly selective alpha-2 receptor agonist with sedative, anxiolytic, and analgesic effects in children [6]. Dexmedetomidine administration can be intranasal, which is advantageous when attempting to sedate uncooperative children such as those diagnosed with ASD. Dexmed also presents minimal cardiorespiratory depression and minimal recovery-related agitation. For these reasons, this drug has gained popularity as a sedative agent, and it has been used in outpatient procedures as the sole sedative, providing successful sedation for completing computed tomography (CT) scans, echocardiograms, and ABR testing [7–9].

The purpose of this study is to describe our outcomes using a novel Dexmed-CH sedation protocol on ASD patients undergoing ABR. Secondly, we compared its effectiveness and safety with our previous standard sedation protocol using CH alone in a matched group of ASD patients.

2. Methods

Institutional Research and Ethics Board approval was obtained before performing this study.

2.1. Data collection

Audiological and medical charts were reviewed of children who underwent sedated ABR testing from January 2004 to December 2015 (before the protocol change occurred in 2016) and from January 2017 to September 2018 (after the protocol change). The ABR Sedation Record included data relating to the clinical history, indication for ABR, sedation dosage, duration of sedation, observed cardiorespiratory parameters, audiological outcomes, and adverse events identified by the sedation nurse at the time of the test. In addition, any allergies, medication history, and co-morbidities were identified. This data, together with relevant patient demographics, were collected in a secure database for detailed analysis.

The inclusion criteria used were: Confirmed diagnosis of ASD, patients aged $\leq$17 years, and patients who underwent ABR testing at our center using chloral hydrate (from January 2004 to December 2015) or intranasal Dexmedetomidine (from January 2017 to September 2018) as a sedative. We excluded patients with other comorbidities than ASD, which may have affected the patient's cooperation, such as trisomy 21 and cerebral palsy. We also excluded patients with incomplete data.

We identified 39 ASD patients who were sedated using Dexmed between January 2017 and September 2018. Two of them were excluded because of other concomitant comorbidities. Between 2005 and 2012, 725 ABRs were done using exclusively chloral hydrate, which were registered in a database used by Valenzuela et al. in a previous published review from our centre on the usage of chloral hydrate [10]. The 37 ASD patients sedated using Dexmed, with or without CH, were matched based on age and sex with 37 ASD patients who were sedated between 2004 and 2015 using the CH-alone protocol. Matching was performed blind to the outcomes measured or any other clinical data.

2.2. Sedated ABR method

ABRs are routinely conducted for infant and child hearing assessment in our institution. The ABR equipment used in this hospital is the Intelligent Hearing Systems (IHS) (Smart EP, Miami, Florida USA). Sedated ABRs are conducted at our institution's ambulatory outpatient clinic when behavioral audiometry cannot answer clinical questions. Exclusion criteria for sedation include: craniofacial abnormalities resulting in airway difficulties sleep apnea, airway obstruction, severe asthma, severe obesity, between others. Since January 2017, we introduced the use of intranasal Dexmed as an option to achieve sedation in patients who underwent ABR. Before this date, only oral chloral hydrate was available. On appointment day, each child is assessed by a sedation nurse and a Pediatric Otolaryngologist who prescribes an appropriate dosage of oral chloral hydrate sedative and or intranasal Dexmed. Our hospital Sedation Committee recommended a dose for chloral hydrate of 50 mg/kg under the age of 2 years and 75 mg/kg over 2. The maximum single dose is 1000 mg. The intranasal dexmedetomidine dose is 1–3 mcg/kg/dose, maximum 200mcg/dose. In patients who already have taken oral chloral hydrate, the dose used was 2mcg/kg/dose. Patients who receive intranasal Dexmed alone, the dose used was 3mcg/kg/dose. Each nostril can receive a maximum of 100mcg. This protocol was reviewed and approve by our hospital Sedation Committee, which comprises sedation nurses, anesthesiologists and other physicians.

Parents are encouraged to partially sleep-deprive the child the night before the ABR investigation as this is believed to help increase the effectiveness of sedation. Parents are also advised to stop the administration of solid foods 5 h (4 h if the child is under 1 year of age) and clear fluids 2 h prior to ABR appointment.

In the soundproof room, a sedation nurse administers chloral hydrate orally. Patients who refuse the oral medication or if they have any oral intake contraindication, they are initially sedated with intranasal Dexmed instead. The child is then given time to fall asleep with his or her guardians. This period is usually between 30 and 40 min. If the patient who received CH does not sleep or is restless, thereby making the ABR test impossible, intranasal Dexmed is administered as a rescue (Fig. 1). Then a new period of time elapses to allow the patient sleep. Once the child is asleep, he/she is placed on a bed and an Audiologist positions recording sensors on the forehead close to the midline, on each mastoid process posterior to the ear, and on the lateral forehead 3 cm from the non-inverting electrode. The Audiologist then performs the ABR test. Throughout the testing, the sedation nurse is present and monitors the child's vital signs until the test is completed, and the child wakes up. At the end of the ABR, the Audiologist and/or Otolaryngologist discuss the ABR results with the parents. A physician performing other outpatient or office duties, and suitable resuscitation equipment, are nearby throughout the sedation period as a safety precaution.

2.3. Data analysis

Statistical analysis was conducted using SPSS version 21 (SPSS, Chicago, IL, USA). Categorical data were expressed as percentage and the time between the sedation start and the beginning of the ABR between the two cohorts as median and range. The Chi-Squared and Fisher Exact tests were used to compare categorical data, while the paired sample *t*-test was utilized for numerical values, after normality verification. A p-value < 0.05 was considered to be significant.

3. Results

Thirty-seven ASD patients who underwent a sedated ABR using Dexmed between January 2017 and September 2018 were included in the study. The mean age at the time of the test was 47 months, with a range of 24–96 months. 72.9% were males. During this period, Dexmed was used under two different modalities: (1) alone as a first choice in patients who refused to swallow CH or have an oral intake

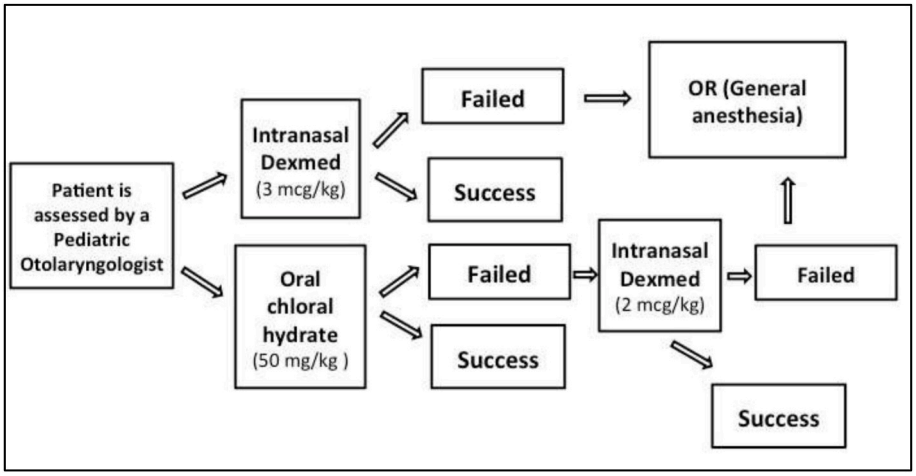

Fig. 1. Intranasal Dexmed-CH protocol used to conduct ABRs in the outpatient clinic.

contraindicated - this occurred in the 24.3% (9/37) of the patients; (2) combined with CH as a rescue when the patient was unable to sleep deeply enough with the oral CH alone - this occurred in the 75.6% (28/37) of the patients.

Seven of nine patients (77.8%) who were sedated using intranasal Dexmed alone had an ABR completed successfully. In patients who received oral CH first and then intranasal Dexmed as a rescue, 26 of 28 (92.8%) were able to complete the ABR. Both groups together had 89% rate of successful sedation (33 of 37). This was better than the successful sedation rate of the matched cohort of 37 ASD patients who were sedated in our hospital using oral CH alone before intranasal Dexmed was included in the protocol, which was 68% (25/37) ($p = 0.024$).

The mean time required for adequate sedation to allow initiation of the ABR test was 41.8 ± 24.5 min (range 15–135 min) under the Dexmed-CH protocol and 35 ± 17.6 min (15–78 min) under CH alone, without a statistically significant difference ($p = 0.124$). There were no major adverse events reported in either cohort. Four patients under the Dexmed-CH protocol had vomiting; in all these cases, vomiting occurred after the patients received the oral CH - a known potential side-effect. In the group which received CH alone, seven patients had vomiting, three patients presented with restlessness, and one patient had prolonged sedation, but without any other consequence. See Table 1.

4. Discussion

As the prevalence and diagnosis of autism is rising [11], the challenge to obtain reliable hearing tests in these patients will be increasing in frequency in our clinical practice. The use of diagnostic ABRs under sedation is currently the gold standard for audiological diagnosis in ASD patients who are unable to reliably complete a behavioral audiometry. Achieving sedation with oral chloral hydrate in uncooperative patients is challenging and often ends in a sedation failure, leading to the need to do the procedure under general anesthesia. In the present study, we demonstrated that the addition of intranasal Dexmed to our oral CH sedation protocol has diminished sedation failure, avoiding the need for general anesthesia in this group of patients. In addition, it has allowed sedation in patients with oral intake contraindications, such as those on a specific oral intake regimen.

Chloral hydrate has been widely used in the sedation of patients in an outpatient scenario because of its safety profile and low cost. Valenzuela at al [10]. reviewed our experiences with ABR sedation using CH over the course of 8 years and found the overall rate of successful sedation to be 95.9%. In that study, the authors also found no significant major adverse events in children sedated with CH. Nevertheless, this success rate decreased when we analyzed the ASD subgroup alone to 68%. This can be explained by several reasons, including the challenge of administrating this drug orally in uncooperative patients, as CH has a pungent odor and a bitter taste.

Since we started our new sedation protocol, intranasal Dexmed has provided benefits in two difficult clinical scenarios. The first is where the patient does not achieve adequate sedation with the maximum dose of oral CH, where intranasal Dexmed was used as a rescue. In addition, Dexmed has been used in patients who are no able to tolerate oral chloral hydrate, as patients who vomit the medication as soon its offered or patients with oral intake contraindication. In these cases, intranasal Dexmed is used as a sole sedative agent. In both scenarios, we have demonstrated than the addition of intranasal Dexmed has avoided sedation failure and the need for general anesthesia to conduct the ABR, and it has increased our global sedation success rate in this group of patients from 68% to 89%.

Intranasal Dexmed is gaining popularity for non-invasive procedural sedation due to its several benefits. Its application is fast and requires only seconds, and no cooperation from the patient is needed. Dexmed is well tolerated and presents minimal cardiorespiratory depression and minimal recovery-related agitation. The intranasal route of drug administration also has benefits: it provides a more reliable delivery of the drug dose even in uncooperative children, avoiding issues if patient spits out or vomits drug dose when this is administered by mouth; also the medication is absorbed across the nasal mucosa more rapidly and avoids the first-pass metabolism of oral medication.

Li et al. [12] published the use of intranasal Dexmed as a rescue after failed sedation using CH in pediatric patients who underwent computed

Table 1
Summary results of the intranasal Dexmed-CH protocol versus the CH alone procedures.

	Intranasal Dexmed-CH	CH	p-value
ABR completed successfully	89% (33/37)	68% (25/37)	P = 0.024
Time required for adequate sedation	41.8 min	35 min	P = 0.250
Major adverse events (apnea, bradycardia)	None	None	
Minor adverse events (vomiting, hypoxemia, prolong sedation, tachypnea)	4 patients vomited (all of them after CH)	7 patients vomited 3 patients presented restlessness 1 prolonged sedation	

Dexmed = Dexmedetomidine; CH= Chloral hydrate; ABR = Audiometry Brainstem Response hearing test.

tomography scanning, ABRs, or visual evoked potentials. Using the same dose applied in our protocol (2mcg/Kg/dose), they achieved a 96.2% of success in healthy children. Zhang et al. [13] also evaluated the use of intranasal Dexmed as a rescue in patients between 1 and 6 months old, who needed an MRI in comparison with an additional dose of oral CH as a rescue. They found better results when intranasal Dexmed was used as a rescue in a 2mcg/Kg/dose (98%) than with lower doses (94% with 1mcg/Kg/dose). They did not find clinically significant hemodynamic disturbance requiring intervention with either dose. Despite our high success rate of 89%, it was slightly lower than the success rates found in these other studies. We could infer that our lower rate of success could be due to the difficulty of sedating autistic children compared to healthy children for multiple reason including challenging behaviors and the need for higher doses in autistic children as they are often older and, therefore, weigh more in comparison. In addition, we only included ASD patients who were previously not successfully sedated using CH and where Dexmed was used as an alternative or as a rescue. We did not include those successfully sedated with CH, and therefore not requiring any Dexmed. We could infer that our success rate would have been higher if we had included these patients.

One of the concerns regarding Dexmed is the high price in comparison with CH. In Canada, a Dexmed vial is approximately $40 Canadian dollars, compared to chloral hydrate approximately $2 per dose. This may mean an increase in the cost of the sedation protocol, and for this reason it was initially implemented only in this specific subset of patients. Nevertheless, if we consider that we are avoiding conducting the ABR under general anesthesia in the operation room, and avoiding failed attempts, the cost difference may no longer be relevant, and therefore, we have expanded its use as a first line in most cases. Similarly, other measures to reduce costs could be implemented, such as splitting vials between patients as other institutions have proposed. However, strict safety protocols should be followed, and this should be implemented in agreement with the hospital's medication policy. Furthermore, we did not find any difference between the time needed to initiate the ABR, so it is important to consider that the use of intranasal Dexmed is not faster than oral CH and that we are not expecting to reduce the time to complete a test.

Our study has multiple limitations. Firstly, this was a retrospective study, and therefore, it may be subject to several types of bias, including: selection bias - in that we selected a specific subset of patients based on their condition and the approach used; information bias – with potential errors in recording or recall of data; and reporting bias, amongst others. Secondly, despite using data over multiple years, our series has a limited sample size, and therefore it is possible that some differences were not observed due to lo lack of study power (type 2 error). This may play a role particularly in the detection or comparison of the low incidence side effects or adverse events, which should be assessed in further studies with a larger sample size.

5. Conclusions

In the present study, we demonstrated that sedation using a protocol of intranasal Dexmed alone, or as rescue after oral CH, in the presence of a sedation nurse in an outpatient setting, was reliable method of performing ABR in infants and children with ASD. Intranasal Dexmed may provide sedation sufficient for completing ABR in pediatric patients who initially failed chloral hydrate sedation. In addition, ASD children undergoing sedated ABR with a protocol that includes the option of intranasal Dexmed were proven to have a higher success rate of sedation and ABR completion compared to when sedation was performed with CH alone. Furthermore, we found no evidence to suggest the practice is unsafe. This study may be of significant value to centers worldwide exploring alternatives to general anesthesia for ABR testing in ASD patients.

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